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1 **Improvements in or relating to germicidal compositions**
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COMPLETE SPECIFICATION

Improvements in or relating to Germicidal Compositions

I, HERBERT CHRISTIAN STECKER, a citizen of the United States of America, residing at One Bridle Way, Ho-Ho-Kus, State of New Jersey, United States of America, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

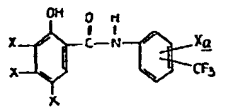
This invention relates to germicidal compositions containing certain halogenated salicylanilides having the trifluoromethyl group as a substituent. More specifically, it relates to germicidal compositions containing salicylanilides having a trifluoromethyl group in the anilide portion of the molecule and one to three non-adjacent halogen substituents which are also non-adjacent to the trifluoromethyl radical.

Halogen - substituted salicylanilides are known in the art as germicides. Among the most potent of these compounds are the 3, 5, 4¹-trihalo salicylanilides. In the art, the trifluoromethyl group has not been considered as having any particular germicidal-enhancing activity. In fact, no particularly special germicidal effect in this grouping is known to have been established.

We have now found that the addition of a trifluoromethyl group in a specific position on the anilide radical greatly increases the germicidal effect of one or two halogens present in specific positions on the salicyl and anilide radicals. In fact, the compounds so formed are much more potent than even the best of the polyhalogenated salicylanilides, such as the 3, 5, 4¹-trihalo compounds.

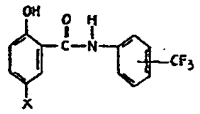
Accordingly, the invention consists in a germicidal composition comprising a substantially germicidally inert material and at least 0.001% by weight of a compound embraced by the formula:

[*Price 4s. 6d.*]

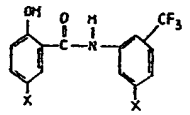


where X is a hydrogen-substituting atom consisting of a halogen atom selected from chlorine, bromine and iodine, and a is a number, ranging from 0 to 2, said compound containing one to three halogen atoms none of which is positioned adjacent the CF_3 group and, when containing more than one halogen atom, none of the halogen atoms being positioned adjacent to each other.

Of particular value in the compositions of the present invention are the compounds embraced by the formula:



and also compounds embraced by the formula:



Hereafter, the trifluoromethyl group will be referred to herein by the symbol "TFM", and the salicylanilide base will be referred to as "SA". Among the preferred compounds, employed in the compositions of the present invention, there are included 5-chloro-3¹-TFM

SA, 5-bromo-3¹-TFM SA, 5-chloro-2¹-TFM SA, 3,5-dibromo-3¹-TFM SA, 5-iodo-3¹-TFM -5¹-chloro SA, 4-bromo-3¹TFM SA, 4-chloro-3¹-TFM SA, 5-iodo-3¹TFM SA, 3,5-diiodo-2¹-TFM SA, 4¹-bromo-5-iodo-2¹-TFM SA, and 3 - chloro - 5 - bromo - 4¹ TFM SA, and mixtures thereof.

The aforesaid TFM salicylanilides may be prepared by the method disclosed in U. S. prepared by heating 5 - chlorosalol with 3-trifluoromethyl-5¹chloro-salicylanilide may be prepared by heating 5 - chlorosalol with 3-trifluoromethyl - 5 - chloroaniline to 180° — 220°C. and continuously distilling off the liberated phenol during the process. It is advantageous to use reduced pressure for this distillation and to carry out the procedure in a nitrogen atmosphere. The crude reaction product is dissolved in alcohol to which an equivalent amount of sodium hydroxide is added in the form of approximately 10N aqueous solution. The resulting solution of the sodium salt of 5-chloro-3¹trifluoromethyl-5¹ chlorosalicylanilide then is decolorized with charcoal and neutralized with dilute HCl. The 5-Cl-3¹-TFM-5¹Cl SA thus precipitated is filtered and recrystalized from ethyl alcohol, ethylacetate, or some other suitable solvent.

These germicidal compounds are useful in compositions comprising a substantially germicidally inert material. For example, some soaps and detergents possess a bactericidal action, but such action, relative to those of the compounds of the present invention, is weak and of little effect in comparison with the overall germicidal activity of the compositions. Such soaps and detergents may therefore be considered as substantially germicidally inert. In such compositions, the germicidal compounds may be employed in concentrations as low as 10 p.p.m. although, from a practical point of view, it is desirable to use as much as 50 p.p.m. or 0.001%, by weight, or 0.01%, and as much as 0.1%, or more. The term "germicidal activity" includes inhibiting and killing action against bacteria, fungi and other micro-organisms.

Particularly useful compositions of the present invention are those comprising soaps and detergents, and especially toilet soaps or cosmetic detergents in which the germicidal compounds may be employed in concentrations of 0.1% to 0.5% by weight, or even as much as 1% or more. The term "detergent" employed herein will be used to mean all synthetic and natural surface - active cleansing agents, including cationic detergents, such as dimethyl stearamido-propyl-2-hydroxy-ammonium dihydrogen phosphate, anionic detergents such as commercial soaps, e.g., alkali metal soaps of hydrolyzed natural or synthetic glycerides of fatty and similar organic acids, e.g., sodium and potassium stearates or oleates, ampholytic detergents, such as sarcosine, non-ionic detergents, such as polyoxypropylene polyoxyethylene condensates, natural detergents, such as starches and vegetable gums, and mixtures thereof. The term "soap" employed herein is used in its popular or ordinary meaning, i.e., a cleansing composition prepared from the reaction product of an alkali metal compound such as potassium or sodium hydroxide and a fat or fatty acid, both saturated and unsaturated.

The germicides possess a strong substantive action upon the skin. Thus, they will be retained on the skin for some time even after repeated washings with soap and water, and in so doing, they serve to inhibit the action of odor-forming bacteria.

One valuable use of the germicides is the use thereof to sanitize fibrous material such as cotton gauze, dressings, textiles and paper pulp. The germicides, or compositions comprising the same, are absorbed on the fibrous materials. They also serve as antiseptic agents when incorporated in plastic or rubber compositions, prior to moulding into articles of commerce, such as baby rattles, gloves and food wrappers.

Although the germicides are highly effective when used in the form of one compound or mixtures thereof, they may also be employed in admixture with other germicides or fungicides, particularly when a synergistic effect is obtained.

The following examples illustrate the numerous advantages of the germicidal compositions made in accordance with the present invention:

EXAMPLE I

Bacteriological tests were performed against *Staphylococcus aureus* with a 24-hour culture at 37°. In each case, 0.1% of the appropriate chemical listed below was incorporated in a 1% solution of soap commercially available under the Registered Trade Mark "Ivory" (a neutral white high grade toilet soap consisting of a mixture of 80% sodium soap and 20% potassium soap produced from a 70% tallow and 30% coconut oil glyceride blend) Cotton disks of 10 mm. diam. were steeped in this mixture, thoroughly rinsed, dried, and applied to seeded agar in Petri dishes, and the zones of inhibition were read after 24 hours, the data obtained (average of three tests) being as follows:-

Compound	Zone of Inhibition (mm)
5,2¹dichloro SA	15.0
5,3¹-dichloro SA	18.5
5,4¹-dichloro SA	21.0
5,2¹,5¹-trichloro SA	21.5
5-chloro-3¹TFM SA	26.0
Control	0.0

It will be noted that the TFM compound employed in the present invention exhibited much higher potency against *Staphylococcus*

aureus than any of the di- or tri-halo SA compounds.

EXAMPLE 2

In this test, each compound listed below was formulated with "Ivory" brand soap so that, on making an aqueous solution containing 8% by weight of soap, the indicated concentrations of compound were obtained. Test cloths then were dipped into each solution, rinsed once in clear water and dried. Disks (10 mm. diam.) of these cloths were placed on agar, seeded with bacteria as indicated, and incubated at 37°C. for 24 hours, the results (average of 3 tests) being as follows: —

(a) E. Coli

Compound Concentration (p.p.m.)	5-Cl-3¹-TFM SA	5-4¹-DiCl SA	3,5,4¹-Tri Cl SA
1600	Slight Zone	No zone; low count under disk	No zone; low count under disk
800	No zone; no count under disk	No zone; high count under disk	No zone; medium count under disk
400	No zone; no count under disk	No zone; high count under disk	No zone; high count under disk

Control: No zone; high count under disk

(b) S. Aureus

1600	29.4 (mm.)	24.0 (mm.)	15.0 (mm.)
800	26.0	19.5	14.5
400	22.5	0.0	14.0

Control: No zone; high count under disk

These data clearly show the high germicidal retention value of the *TFM* compounds employed in the present invention upon dilution, against *S. Aureus* and *E. Coli*, in comparison to typical di- and tri-halogenated SA compounds.

EXAMPLE 3

Pennasay disk tests were run in the same manner as outlined in Example 1 at various compound concentrations (other factors being the same), against *S. Aureus* with the following results: —

Compound Concentration (p.p.m.)	5-Cl-3¹-TFM SA	5,4¹-DiCl SA	3,5,4¹-TriCl SA
800	27.8 (mm.)	18.5 (mm.)	18.6 (mm.)
80	No zone; no count under disk	No zone; moderate count under disk	No zone; moderate count under disk

EXAMPLE 4

Skin substantivity (leaching) tests were conducted by applying aqueous solutions (in compound concentrations specified) to fresh calfskin (free of wrinkles) and subjecting the treated skin to clear water leaching for 5 minutes. In performing this test, a section of fresh calfskin (about 3" x 4" is subjected to a

washing procedure in the same manner as the back of the hand might be washed using the treated soap either in liquid form or as a lather. The treated skin then is rinsed thoroughly with moderate rubbing in a manner similar to washing the hands.

When this treatment is completed, disks are cut out of the center portion of the calf-skin pieces with an instrument such as a sterile cork borer. The resulting disks then are placed on nutrient agar with the epidermis side down, the agar previously being seeded with *Staphylococcus* aureus, After incubation at 37°C. for 24 hours, zones of inhibition (average of 3 tests) are read and compared with the controls, the data obtained being as follows:—

Compound Concentration (p.p.m.)	5-Cl-3¹-TFM SA	5,4¹-DiCl SA	3,5,4¹-TriCl SA
800	29.8 (mm.)	20.5 (mm.)	21.2 (mm.)
400	26.6	18.2	21.0
80	19.8	Very strong growth	Very strong growth
40	Slight growth	»	»

EXAMPLE 5

Standard toxic dilution tests were made against two organisms, using "Ivory" brand soap to which had been added 1% by weight of compound specified. The indicated dilutions, made from the stock soap solution, gave the following results (average of 3 tests):—

Compound	E. Coli Dilution (p.p.m.) 50	25	10	5
Control	TNTC*	TNTC	TNTC	TNTC
3,5,4-TriCl SA	TNTC	TNTC	TNTC	TNTC
3,5-DiCl-3¹-TFM-4¹Cl SA	TNTC	TNTC	TNTC	TNTC
Tetramethyl thiuram disulfide (TMTD)	0	TNTC	TNTC	TNTC
Hexachlorophene ("G-11" brand)	0	0	TNTC	TNTC
5,4¹DiCl SA	0	0	35	TNTC
5,4¹DiBr SA	0	0	29	TNTC
5-Cl-3¹-TFM SA	0	0	0	160
5-Br-3¹-TFM SA	0	0	0	120
3,5-DiBr-3¹-TFM SA	0	0	0	110
5-Cl-2¹-TFM SA	0	0	0	100
5-I-3¹-TFM-5¹Cl-SA	0	0	0	0

*TNTC = Too numerous to count

The above data show that the only compounds effective in 10 p.p.m. dilution were those employed in the present invention, the most effective being 5-iodo-3¹trifluoromethyl-5¹-chloro salicylanilide. The data also show that trifluoromethyl compounds containing a halogen adjacent to the TFM group are much less active toward *E. Coli* than similar homologs in which the halogen is not adjacent.

EXAMPLE 6

Toxic dilution tests were made as in Example 5, against *S. Typhi*, with the following results:—

Compound	S. Typhi Dilution (p.p.m.)			
	50	25	10	5
Control	TNTC	TNTC	TNTC	TNTC
5,4'-DiCl SA	TNTC	TNTC	TNTC	TNTC
3,5,4'-TriClSA	TNTC	TNTC	TNTC	TNCT
3,5,DiCl-3'-TFM-4'Cl SA	TNTC	TNTC	TNTC	TNTC
TMTD	0	8000	TNTC	TNTC
5-Cl-3'-TFM SA	0	0	250	10,000
5-Cl-2'-TFM SA	0	0	230	8,500
5-Br-3'-TFM SA	0	0	225	8,000
5-I-3'-TFM SA	0	0	200	9,000
3,5-DiBr-3'-TFM SA	0	0	100	4,000
3,5,2'-TriCl-4'-TFM SA	0	0	100	3,000
3,5,5'-TriCl-3'-TFM SA	0	0	50	1,000

Again, in this series, the compounds employed in the present invention were the only ones which were effective completely at 25 p.p.m. concentration. One of the most effective compounds in this case was 3,5-dibromo-3'-trifluoromethyl salicylanilide. Addition of a chlorine in the 4' position to this compound practically killed its potency.

EXAMPLE 7

Pennasay disk tests were run as outlined in Example 1, with the exception that the germicidal compound was used in 1% concentration (on the soap weight basis), and the soap-germicide concentration was 5% on the basis of the water weight, thus providing a final germicide concentration of 0.0005%. The data obtained were as follows (average of 6 replicates):

Compound	L. Casei* Inhibition Zone, mm.
Hexachlorophene ("G-11" brand)	15.5
5,4'-DiCl SA	15.5
5-Cl-3'-TFM SA	17.0
Control	0.0

*Microinoculum; 1% inoculum on disk.

Here again, the TFM compound of the present invention proved to be superior against *L. Casei* when compared against commercial germicides.

EXAMPLE 8

This test involved the deep broth culture method wherein a standard clear sterilized beef broth is used, to which is added one of the compounds to give the final concentrations as indicated. These compound solutions were inoculated with *E. Coli*, incubated for 24 hours at 37°C., and observed for the presence of organism growth as exhibited by development of cloudiness or haze in the beef broth. The results obtained were as follows (growth indicated by "+", no growth by "0"):—

Compound	Dilution (p.p.m.) 50	25	10	5
Control	+	+	+	+
Hexachlorophene	0	0	+	+
5,4'-DiCl SA	0	0	+	+
5-Cl-3'-TFM SA	0	0	0	+
3,5,2'-TriCl-4'-TFM SA	0	0	0	+
3,5,5'-TriCl-3'-TFM SA	0	0	0	+

The TFM compounds employed in the present invention were the only germicides effective in 10 p.p.m. dilution.

EXAMPLE 9

Pooled saliva toxic dilution tests were run as in Example 5 with the exception that pooled saliva was used in place of water for dilution. The results obtained were as follows:—

Compound	Dilution (p.p.m.) 50	25	10
Control	+	+	+
4,2',4',6'-Tetra Br SA	+	+	+
3,4-DiBr-3'-TFM SA	+	+	+
5,3'-4'-TriBr SA	+	+	+
4-Cl-3'-TFM-4'-Cl SA	+	+	+
4,3'-DiBr SA	0	0	+
5,3'-DiBr SA	0	0	+
5,3'-DiCl SA	0	0	+
4,3'-DiCl SA	0	0	—
5,3'-DiI SA	0	0	+
4-Br-3'-TFM SA	0	0	0
5-Br-3'-TFM SA	0	0	0
5-Cl-3'-TFM SA	0	0	0
4-Cl-3'-TFM SA	0	0	0
5-I-3'-TFM SA	0	0	0
3,5-DiBr-3'-TFM SA	0	0	0
3,5,2'-TriCl-4'-TFM SA	0	0	0
3,5,5'-TriCl-3'-TFM SA	0	0	0

It will be noted again that only the TFM compounds without said adjacent substituent positions were effective at 10 p.p.m. dilution. Also, the tests show that TFM compounds having adjacently disposed halogens (other than in the TFM group), such as 3,4-dibromo-3'-trifluoromethyl SA, possess no germicidal effectiveness at the indicated dilutions.

EXAMPLE 10

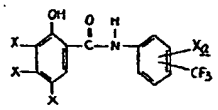
Pennasay cotton disk tests were run as in Example 5 on the compounds listed, and the following results were obtained (triplicate averages):—

Compound	S. Aureus Zone of Inhibition (mm.)
Control	0.0
4,2¹,4¹,6¹-TetraBr SA	13.4
5,3¹,4¹,-TriBr SA	13.5
4-Cl-3¹TFM-4¹-Cl SA	14.5
3,4-DiBr-3¹-TFM SA	15.0
4,3¹-DiCl SA	25.1
4,3¹-DiBr SA	25.2
5,3¹-DiCl SA	25.2
5,3¹-DiI SA	25.2
5,3¹-DiBr SA	25.3
4-Cl-3¹-TFM SA	27.9
5-Br-3¹-TFM SA	28.1
5-I-3¹-TFM SA	28.1
3,5-DiBr-3¹-TFM SA	28.2
5-Cl-3¹-TFM SA	28.2
4-Br-3¹-TFM SA	28.3
3,5,5¹-TriCl-3¹-TFM SA	28.3
3,5,2¹-TriCl-4¹-TFM SA	28.4

Also in this case, it will be noted that the TFM compounds without halogens adjacent to the TFM group exhibited the highest germicidal effect. The relative ineffectiveness of compounds having a halogen adjacently disposed to the TFM group, as exhibited by 4 - Chloro - 3¹ - trifluoromethyl - 4¹ - chloro salicylanilide, also is observable.

WHAT I CLAIM IS:—

1. A germicidal composition comprising a substantially germicidally inert material and at least 0.001% by weight of a compound embraced by the formula:



where X is a hydrogen-substituting atom consisting of a halogen atom selected from chlorine, bromine and iodine, and *a* is a number ranging from 0 to 2, said compound containing one to three halogen atoms none of which is positioned adjacent the CF_3 group and, when containing more than one halogen atom, none of the halogen atoms being positioned adjacent to each other.

2. A germicidal composition as set forth in Claim 1, in which the substantially germicidally inert material is a detergent as hereinbefore defined.

3. A germicidal composition as set forth in Claim 1 or 2, in which at least 0.01% of the compound embraced by the formula in Claim 1 is included.

4. A germicidal composition as set forth in Claim 1, 2 or 3, in which the compoumd embraced by the formula in Claim 1 is 5-chloro-3¹trifluorumethyl salicylanilide.

5. A germicidal composition as set forth in Claim 1, 2 or 3, in which the compound embraced by the formula in Claim 1 is 5-bromo-3¹-trifloromethyl salicylanilide.

6. A germicidal composition as set forth in Claim 1, 2 or 3, in which the compound embraced by the formula in Claim 1 is 5-iodo-3¹-trifluoromethyl salicylanilide.

7. A germicidal composition as set forth in Claim 1, 2 or 3, in which the compound embraced by the formula in Claim 1 is 3,5-dibromo-3¹-trifluoromethyl salicylanilide

8. A germicidal composition as set forth in Claim 1, 2 or 3, in which the compound embraced by the formula in Claim 1 is 5 - chloro - 3¹ - trifluoromethyl - 5¹ - chloro salicylanilide.

9. A germicidal composition according to claim 2 comprising a detergent and a compound embraced by the formula in Claim 1, substantially as hereinbefore described.

10. A germicidal composition according to any preceding claim absorbed on a fibrous material.

11. A germicidal composition according to Claim 1, substantially as hereinbefore described.

12. A compound embraced by the formula in Claim 1 absorbed on a fibrous material.

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